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22

Please find below and/or attached an Office communication concerning this application or proceeding.

Prosecution is hereby reopening since the suspension period has expired.

The specification has been amended, claims 1, 20, 27 have been amended, claims 125-120 have been added by the amendment dated January 28, 2002.

Claim 1 has been amended by the response filed March 29, 2001.

Claims 29, 47, 66, 73, 77, 81, 85, 89, 93, 109, and non-elected species (species of claims 9, 11, 13 and 23) remain withdrawn from consideration, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Elected claims 1-10, 12, 14-22 and 24-28 readable on species of 5' X1X2CGX3X4 3' wherein X1 is G, X2 is T, X3 is T, and X4 is T as a species of CpG motif, the species of colloidal dispersion system, the species of alum as non-oligo mucosal adjuvant, the species of subject at risk of developing an infectious disease, the species of infectious virus as a species of antigen, the species of intranasal route, to which the following grounds of rejection are applicable, are pending.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-10, 12 and 14-22, 24-28, 125-130 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method for inducing a mucosal immune response, comprising:

Administering intranasally to a mucosal surface of a subject an effective amount for inducing a mucosal immune response of an oligonucleotide having a length of least 8 nucleotide residues and comprising CpG motif containing oligonucleotide including the elected species of 5' X1X2CGX3X4 3' wherein both C and G are unmethylated; and administering to the subject an

antigen not encoded in a nucleic acid vector to the subject to induce the mucosal immune response, does not reasonably provide enablement for methods of administering any CpT motif containing oligonucleotide of less than 8 nucleotide residues including the elected species of 5' X1X2CGX3X4 3' wherein X1 is G, X2 is T, X3 is T, and X4 is T for inducing a mucosal immunity to a recombinant peptide/polypeptide antigen within the context of therapeutic applications. The as-filed specification is also not enabling for a method of inducing a mucosal immunity wherein the subjected treated with the oligonucleotide is just simply passively waited for any period of to time to be exposed to an antigen which is not encoded in a nucleic acid vector.

With respect to the preamble of claim 1 and claims dependent therefrom, the presently pending claims encompass a method of "exposing" any subject including mammals, insects, reptiles, birds that is at risk of developing an infectious disease, *e.g.,* viral infection, it is apparent to a skilled artisan on the basis of applicant's disclosure that in order to carry out the invention, the administered nucleic acid or oligo containing a CG motif must necessarily by itself induces a sufficient mucosally therapeutic response at any subsequent period at which the treated subject is simply passively exposed to an antigen, *e.g.,* by simply inhalation or eating or skin contact, for example. No working examples are provided for this particular claimed embodiment. No data from either the as-filed specification or the prior art are provided to illustrate this particular embodiment. As evidenced by numerous arts cited in the IDS, for example all of the publications authored by Heather Davis or McCluskie, teach that CpG (wherein both CG are unmethylated) containing oligos are known to be an effective adjuvant when administered together with a sufficient amount of antigen or shortly prior or after an active administration of an effective dose of antigen, and that oligos are not simple drugs and intrinsically posses degradation properties in an in vivo environment. Furthermore, at about the filing date of the present application, both Krieg et al. (Trends in Microbiology 6:23-27, 1998; IDS) and McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999) have noted that the route of administration and DNA dose (for this instance, oligonucleotides having the recited core structure) as well as other factors such as the antigen, the dose of antigen, the co-expression of cytokines, and whether other adjuvant is used are also involved in determining the types of host immune responses elicited (page 313, see the section

titled "Role of CpG immunostimulatory sequences). As such, given the complexity and variable factors that interplay during an administration of a CpG motif containing oligonucleotide, and given the breadth of the claimed invention, wherein the claimed oligo can be reasonably interpreted as a preventive drug for immunization in any subject so as to elicit any preventive response to any passive exposure by any subject to an allergen or antigen, it is not apparent how a skilled artisan to determine, without any undue experimentation, as to which particular among an enormous number of claimed oligos, and/or as to which particular antigen and/or method steps can be used effective so as to generate a prophylactically mucosal response as contemplated by applicants at the time the invention was made, particularly when considered all o the Wands factors as a whole.

With respect to the breadth of the claimed invention which clearly embraces any oligonucleotide wherein only C is need to be unmethylated when present in the CG dinucleotide, the totality of the prior art (also cited by the IDS, which includes McCluskie references, Krieg references, and Davis references and issued patents authored by any of the mentioned authors) clearly teach that CpG motifs are needed to be unmethylated, and that the unmethylated CpG containing oligo of at least 8 nucleotides and its flanking residues are critical for is immunostimulatory activity, let alone its specifically claimed mucosal immunostimulatory activity. McCluskie (1998, The J. of immunology, 161:4463-4466) and Moldoveanu (Vaccine 16, 1216, 1998) are cited to illustrate the importance of the presence of CpG motif wherein both C and G nucleotides are unmehtylated) in order to elicit an mucosal immunity when administered together with a recombinant antigen.

With respect to the issue of route of administrations which must exhibit a mucosally therapeutic or prophylactic response, the claims encompass a method for inducing a prophylactically or therapeutically mucosal immunity to an antigen in any host by introducing the claimed oligo/antigen or just the oligo alone of the presently claimed invention into any host mucosa by any route of administration. The instant specification is not enabled for such a broadly claimed invention. This is because apart from the exemplification showing that a desired induced mucosal immunity can be attained with a recombinant hepatitis surface antigen mixed with or

conjugated to the elected oligo with CG both being unmethylated via intranasal route, the instant specification fails to provide sufficient guidance for one skilled in the art on how to attain the same desired induced mucosal immunity by the same composition at any other mucosal sites via other routes of delivery. Furthermore, at about the filing date of the present application, both Krieg et al. (Trends in Microbiology 6:23-27, 1998; IDS) and McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999) have noted that the route of administration and DNA dose (for this instance, oligonucleotides having the recited core structure) as well as other factors such as the antigen, the dose of antigen, the co-expression of cytokines, and whether other adjuvant is used are also involved in determining the types of host immune responses elicited (page 313, see the section titled "Role of CpG immunostimulatory sequences). As such, with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for one skilled in the art to make and use the full scope of the methods as claimed.

Moreover, the physiological art is recognized as unpredictable (MPEP 2164.03). As set forth in *In re Fisher*, 166 USPQ 18 (CCPA 1970), compliance with 35 USC 112, first paragraph requires:

> That scope of claims must bear a reasonable correlation to scope of enablement provided by specification to persons of ordinary skill in the are; in cases involving predictable factors, such as mechanical or electrical elements, a single embodiment provides broad enablement in the sense that, once imagined, other embodiments can be made without difficulty and their performance characteristics predicted by resort to known scientific laws; in cases involving unpredictable factors, such as most chemical reactions and physiological activity, scope of enablement varies inversely with degree of unpredictability of factors involved.

Nothwitstanding the lack of working examples and the breadth of the claims with respect to non-intranasal route, at the effective filing date of the present application, the induction of mucosal immunity by a stimulatory nucleic acid molecule having the recited core nucleotide sequence in the presence of an antigen has not been demonstrated for any other mucosal routes such as oral, vaginal and intrarectal routes. A number of studies have shown that the route of mucosal immunization can influence both the strength and nature of immune response, as evidenced by the teachings of Rudin et al. (Infection and Immunity 66:3390-3396, 1998) Kleanthous et al. (Infection and Immunity 66:2879-2886, 1998), Krieg et al. (Trends in

Microbiology 6:23-27, 1998; IDS) and McCluskie et al. (Crit. Rev. Immunol. 19:303-329, 1999). The totality of the art of record teaches that the route of administration and DNA dose (for this instance, oligonucleotides having the recited core structure) as well as other factors such as the antigen, the dose of antigen, the co-expression of cytokines, and whether other adjuvant is used are also involved in determining the types of host immune responses elicited (page 313, see the section titled "Role of CpG immunostimulatory sequences). Krieg et al. (Trends in Microbiology 6:23-27, 1998; IDS) specifically teach "It has been noted that gene-gun administration of DNA vaccines (intradermal) is associated with a relatively stronger Th2 response to the antigen, whereas i.m. injection of DNA vaccines is associated with a Th1 response. One explanation for this finding is that the dose of DNA used in gene gun vaccination may provide a relatively weak Th1 signal, whereas i.m. injection of CpG motifs provides a strong signal for the Th1 response. However, recent studies suggest that neither DNA dose nor an intradermal route of administration alone can explain the predominance of Th2 responses following gene-gun vaccination" (page 25, col. 2, first full paragraph). Therefore, it is apparent that with the lack of sufficient guidance provided by the present application, it would have required undue experimentation for one skilled in the art to make and use the full scope of the methods as claimed, especially for attaining specific desired results such as the level of sIgA produced in the host in response to an active introduction of the antigen alone into the mucosal tissue, let alone claimed embodiments which embrace a passive exposure to any antigen by any host. Note also applicant's response (page 13-14) which clearly argues that oral administration of a CpG containing oligo as those disclosed in the Krieg reference (WO96/02555) would not generate a mucosal immunity, at yet, the claims embrace any route of administration so as to deliver any of the claimed oligo to a mucosal surface.

Accordingly, due to the lack of guidance provided by the specification regarding to the issues set forth above, the unpredictability of the physiological, and the breadth of the claims, it would have required undue experimentation for one skilled in the art to make and use the instant broadly claimed invention.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless --
>
> b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

Claims 1-10, 12, 14-22, 24-28, 125-130 are rejected under 35 U.S.C. 102(e) as being anticipated by Krieg *et al.* (US Pat No. 6,218,371), as evidenced by Moldoveanu *et al.,* Vaccine 16, p. 1216, 1998, Sato *et al.* (US Pat No. 6,090,791), McCluskie *et al.* (IDS, C2), and Mestecky *et al.* (Genetically Engineered Vaccines, 1992, IDS, C33).

The essential feature of the presently pending claims is that a mucosal immunity would be elicited by a combination administration to the mucosal surface of any subject, *e.g.,* oral administration or intranasal administration, of any known antigen (not in the form of a nucleic acid sequence) and an oligonucleotide (which can be complexed with any known colloidal dispersion system including lipid based system) having a length of least 8 nucleotide residues and comprising CpT motif containing oligonucleotide including the elected species of 5' X1X2CGX3X4 3' wherein X1 is G, X2 is T, X3 is T, and X4 is T. Krieg *et al.* teach the same throughout the disclosure (columns 15, 18-20, 23-28, 31 and 32). More specifically, on column 31, oral administration and nasal administration of the oligo and/or antigen is disclosed. CpG motifs including 5' GTCpGTT is also disclosed on columns 3, 4 and 23. The use of a colloidal dispersion system is disclosed on column 19. The use of a cytokine including B-7 as an adjuvant in combination with the CpG containing oligo of at least 8 nucleotides is disclosed on column 25, 26 and 29, for example. IL-6 production is also disclosed on Example 7. In view of the

factual evidence established by Moldoveanu *et al.,* Vaccine 16, p. 1216, 1998, Sato *et al.* (US Pat No. 6,090,791) McCluskie *et al.* (IDS, C2) which shows that CpG motifs when administered to the mucosal surface of a subject does generate an mucosal immunity, and by Mestecky *et al.* which demonstrate local production of IL-6 at the mucosal surface does stimulate production of IgA antibodies, the method of Krieg *et al.* would inherently generate production of mucosal immunity, particularly in view of the absence of evidence to the contrary.

Applicant's response states that the submitted 131 Declaration is sufficient to overcome the above rejection. However, given that the Declaration does not any factual evidence to demonstrate the claimed invention as a whole was conceived of and reduced to practice prior to the effective filing date of US 6,21,371. As such, until proper corroborative support is submitted, the rejection as indicated above and below wherein the '371 patent is employed as the primary reference remains proper and is maintained for the reasons of record.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-10, 12, 14-22 and 24-28, and 125-130 are rejected under 35 U.S.C. 103 as being unpatentable over Krieg *et al.* (US Pat No. 6,218,371), taken with Krieg *et al.* (Trends In Mircobiology, Vol. 6, No. 1, pp. 23-27, 1998), as evidenced by Moldoveanu *et al.,* Vaccine 16, p. 1216, 1998, Sato *et al.* (US Pat No. 6,090,791), McCluskie *et al.* (IDS, C2), and Mestecky *et al.* (Genetically Engineered Vaccines, 1992, IDS, C33).

The rejection of claims 1-7, 10, 12, and 14-22 and 26-27, as being anticipated by either Krieg *et al.,* as evidenced by Moldoveanu *et al.,* Vaccine 16, p. 1216, 1998, Sato *et al.* (US Pat No. 6,090,791), McCluskie *et al.* (IDS, C2), and Mestecky *et al.* (Genetically Engineered Vaccines, 1992, IDS, C33), is applied here as indicated above. To the extent that the references do not teach the use of Th2 response induced-adjuvant including alum in the methods, Krieg (Trends In Mircobiology) is one of many references which teach that alum is effective as an Th2 response induced adjuvant which is the only one approved for human use in combination with antigen vaccines.

Thus, it would have been obvious for one of ordinary skill in the art to have employed alum in the immunization methods of either Krieg or Krieg *et al.* One of ordinary skill in the art would have been motivated to have employed alum as an adjuvant in the methods of Krieg or Krieg *et al.* because Krieg (Trends In Mircobiology) is one of many references which teach that alum is effective as an Th2 response induced adjuvant which is the only one approved for human use in combination with antigen vaccines. Note that it is well established that an mucosal immunity the same as Th2 response.

Thus, the claimed invention as a whole was *prima facie* obvious.

Claims 1-10, 12, 14-22, 24-28, and 125-130 are rejected under 35 U.S.C. 103(a) as being unpatentable over Briles et al. (U.S. Patent No. 6,042,838) in view of Krieg et al. (U.S. Patent No. 6,194,388; IDS, or WO96/02555), and Hodes (Fundamental Immunology, 2ed., pages 587-620, 1989).

Briles et al. disclose an immunogenic composition and a method for eliciting an immunological response against pneumococcal surface protein A (PSPA) in a host susceptible to *Streptococcus pneumoniae* by intranasally administering to the host an effective amount of PSPA in the form of a killed whole pneumococci, a lysate of pneumococci or an isolated PSPA or an

immunogenic fragment thereof in the presence of an adjuvant, with cholera toxin B as a preferred adjuvant, to protect a host against pneumoccocal colonization and/or systemic infection (see summary of invention, col. 1-7). Briles et al. also teach that immunostimulatory agents or adjuvants have been used to improve the host immune responses to vaccines, these include intrinsic adjuvants such as lipopolysaccharides which normally are the components of the killed or attenuated bacteria used as vaccines or extrinsic adjuvants such as aluminum hydroxide, LPS, Freund's complete adjuvant and others which are immunomodulators which are typically non-covalently linked to antigens and are formulated to enhance the host immune responses. Briles further disclose that the immunogenic composition can be prepared as inhalables, sprays and that pump spray or nasal spray or squeeze dispensers (a device) for dispensing a metered dose or a dose with a particular particle or droplet size are commercial available for mucosal administration (col. 3, lines 32-52). Briles et al. further teach that useful surfactants for the immunogenic composition include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Tween 80, Polyoxyl 40 Stearate and others to enhance absorption (col. 6, lines 14-21). Briles et al. further teach that specific IgA antibodies are induced in secretions of the intestinal, respiratory, and genital tracts, as well as predominantly IgA antibody secreting cells in the intestinal lamina propria and salivary glands. Strong circulatory immune responses are also induced with IgG and IgA antibodies in the serum, and IgG and IgA antibody-secreting cells in the spleen (col. 8, lines 14-34, and examples). Briles et al. do not teach the use of any immunostimulatory oligonucleotide, including a core nucleotide sequence having the formula: 5'-Purine-Purine-[C]-[G]-Pyrimidine-Pyrimidine-3' or one having the core nucleotide sequence of the elected species as an adjuvant in a composition or a method for inducing mucosal immunity to an antigen in a mammalian host via intranasal administration.

However, at the effective filing date of the present application, Krieg et al. disclose various immunostimulatory oligonucleotides having the CpG motifs, among which is an oligonucleotide comprising the sequence AACpGTT and GTCpGTT (see Table 1). For facilitating uptake into cells, the immunostimulatory oligonucleotides are preferably in the range of 8 to 40 base pairs in size (col. 6, lines 18-20). Additionally, Krieg et al. teach that the immunostimulatory

oligonucleotides can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims). Krieg et al. further teach that *in vivo* and in whole spleen cells studies, unmethylated CpG oligonucleotides produce no significant increase in IL-2, IL-3, IL-4 or IL-10 within the first six hours, whereas increased expression levels of IL-6, interferon-gamma and IL-12 were detected (col. 14, lines 34-46). Hodes teaches that IFN production is associated with the Th1 T cell subset (see Table 3) and that increased gamma interferon enhances IgG2a responses while suppressing IgG2b, IgG1 and IgG3 responses, the latter of which are associated with Th2 T cell subset stimulation (page 598, col. 1, first full paragraph). Hodes also teaches that IgE production, the isotype primarily involved in allergic reactions, is associated with a Th2 response. It is apparent from the totality of the combined cited reference plus the knowledge available the totality of the prior art of recordthat oligonucleotides comprising the sequence AACGTT or GTCGTT effect a shift in an immune response from a Th2 phenotype to a Th1 phenotype.

Accordingly, it would have been obvious for an ordinary skilled artisan, particularly an investigator in the art of vaccine, to modify the immunogenic composition (including a kit that has pump spray or nasal spray or squeeze dispensers for dispensing a metered dose or dose with a particular size of the immunogenic composition) and the method for inducing mucosal immunity against pneumococcal colonization and systemic infection taught by Briles et al. by utilizing an immunostimulatory oligonucleotide having the CpG motif as taught by Krieg et al. in either a free form or in a non-covalently linkage with PSPA antigens as an adjuvant (It is noted that it is well known in the art of vaccine that antigen is normally conjugated to an adjuvant to enhance the host immune response as also evidenced by the teachings of Briles et al.) . One of ordinary skilled artisan would have been motivated to carry out the above modification simply because Krieg et al. clearly teach that an immunomodultory oligonucleotide having a CpG motif can be used in conjunction with a vaccine or an antigen in a pharmaceutically acceptable carrier, as an adjuvant to boost a mammal's immune response to effect better response from the vaccine (col. 17, line 65 continues to line 3 of col. 18; and the claims). In addition, due to the immune effects of

unmethylated CpG oligonucleotides comprising any of the disclosed and claimed CpG motif generated *in vivo*, in whole spleen cells and human peripheral blood lymphocytes taught by Krieg et al. and Yamamoto et al., an ordinary skilled artisan would recognize that the oligonucleotides can effect a shift in an immune response from a Th2 phenotype to a Th1 phenotype based on the cytokine profile associated with Th1 and Th2 immune responses taught by Hodes. Since the modified composition and the step(s) of the modified method based on the combined teachings Briles et al., Krieg et al., and Hodes are indistinguishable from the composition and the step(s) of the methods being claimed by the present application, the specific recited immune effects (e.g., the level of sIgA production induced in the host would be attained and not be unexpected.

Therefore, the claimed invention as a whole was *prima facie* obvious in the absence of evidence to the contrary.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Clark*, may be reached at **(703) 305-4051.**

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

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